Treatment recommendations for extrapyramidal side effects associated with second-generation antipsychotic use in children and youth

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BACKGROUND/OBJECTIVE: Antipsychotic use in children is increasing. The purpose of the present article was to provide guidance to clinicians on the clinical management of extrapyramidal side effects of second-generation antipsychotics.

METHODS: Published literature, key informant interviews, and discussions with panel members and stakeholder partners were used to identify key clinical areas of guidance and preferences on format for the present recommendations. Draft recommendations were presented to a guideline panel. Members of the guideline panel evaluated the information gathered from the systematic review of the literature and used a nominal group process to reach a consensus on treatment recommendations. A description of the neurological abnormalities commonly seen with antipsychotic medications is provided, as well as recommendations on how to examine and quantify these abnormalities. A stepwise approach to the management of neurological abnormalities is provided.

RESULTS: Several different types of extrapyramidal symptoms can be seen secondary to antipsychotic use in children including neuroleptic-induced acute dystonia, neuroleptic-induced akathisia, neuroleptic-induced parkinsonism, neuroleptic-induced tardive dyskinesia, tardive dystonia and tardive akathisia, and withdrawal dyskinesias. The overwhelming majority of evidence on the treatment of antipsychotic-induced movement disorders comes from adult patients with schizophrenia. Given the scarcity of paediatric data, recommendations were made with reference to both the adult and paediatric literature. Given the limitations in the generalizability of data from adult subjects to children, these recommendations should be considered on the basis of expert opinion, rather than evidence based.

CONCLUSION: Clinicians must be aware of the potential of second-generation antipsychotics to induce neurological side effects, and should exercise a high degree of vigilance when prescribing these medications.

Key Words: *Antipsychotic medications; Children; Extrapyramidal side effects*

Les recommandations thérapeutiques relatives aux effets secondaires extrapyramidaux associés à l'utilisation d'antipsychotiques de deuxième génération chez les enfants et les adolescents

HISTORIQUE ET OBJECTIF : L'utilisation d'antipsychotiques augmente chez les enfants. Le présent article visait à orienter les cliniciens quant à la prise en charge clinique des effets secondaires extrapyramidaux des antipsychotiques de deuxième génération.

MÉTHODOLOGIE : Les publications, les entrevues avec des informateurs clés et des échanges avec les membres d'un groupe de discussion et les partenaires ont permis de déterminer les principaux secteurs cliniques d'orientation et les préférences quant à la structure des présentes recommandations. Les membres responsables des lignes directrices ont reçu le projet de recommandations, ont évalué l'information recueillie grâce à une analyse bibliographique systématique et ont utilisé un processus de groupe nominal pour parvenir à un consensus quant aux recommandations thérapeutiques. Les lignes directrices contiennent une description des anomalies neurologiques souvent observées avec l'utilisation d'antipsychotiques ainsi que les recommandations sur le moyen d'examiner et de quantifier ces anomalies. Une démarche séquentielle sur la prise en charge des anomalies neurologiques est présentée.

RÉSULTATS : On peut observer plusieurs types de symptômes extrapyramidaux attribuables à l'utilisation d'antipsychotiques chez les enfants, y compris la dystonie aiguë, l'akathisie, le parkinsonisme et la dyskinésie tardive, toutes induites par les neuroleptiques, de même que la dystonie tardive, l'akathisie tardive et les dyskinésies de sevrage. La forte majorité des données probantes sur le traitement des troubles du mouvement induits par les antipsychotiques proviennent de patients adultes atteints de schizophrénie. Étant donné le peu de données pédiatriques, les recommandations découlent de publications portant tant sur des adultes que sur des enfants. Compte tenu des limites de généralisation des données provenant de sujets adultes pour des enfants, il faudrait évaluer ces recommandations d'après les avis d'experts plutôt que d'après les données probantes.

CONCLUSION : Les cliniciens doivent savoir que les antipsychotiques de deuxième génération ont le potentiel d'induire des effets secondaires neurologiques et devraient faire preuve d'une extrême vigilance lorsqu'ils en prescrivent.

Second-generation antipsychotics (SGAs) may offer important benefits to children with mental health disorders. In recent years, the use of SGAs in children has expanded to a number of mental health disorders including disruptive and aggressive behaviour, irritability associated with autism-spectrum disorder and mood disorders. As with any medication, adverse effects can be significant, and the benefits and risks of therapy should be considered. The rising use of SGAs in Canada and internationally in children and youth has stimulated the creation of guidelines on monitoring their safety and effectiveness. The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline group has developed evidence-based recommendations

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on monitoring for metabolic and neurological complications of SGAs prescribed to children and youth (1). To assist practitioners who perform these monitoring procedures, we have created a complementary set of treatment recommendations if abnormal measurements or results are encountered. It is expected that as the use of SGAs in children grows, clinicians will encounter more use-related adverse events.

The purpose of the present article is to provide guidance on the clinical management of extrapyramidal side effects (EPS) of SGAs. Note that cognitive side effects of SGAs are not addressed in these guidelines. A description of the EPS commonly seen with antipsychotic medications is provided, as well as recommendations on how to examine and quantify these abnormalities. A stepwise approach to management is provided. The target users of these guidelines are prescribers of antipsychotics for children and youth including psychiatrists, paediatricians, neurologists and family physicians (2). While EPS are not observed as frequently with the use of SGAs in comparison with first-generation antipsychotics, the risk of these side effects is not zero. These medications are labelled 'atypical' in comparison with first-generation antipsychotics based on their chemical properties, which include rapid dissociation from dopamine type 2 receptors and blockade of serotonin type 2A receptors. Many of the SGAs, especially risperidone, olanzapine and aripiprazole, cause neurological side effects. A meta-analysis of 10 randomized controlled trials (RCTs) of risperidone revealed that risperidone-treated children had a significantly higher OR of EPS compared with the placebo group, with an OR of 3.55 (P<0.00001). Ninety-nine of 433 (23%) risperidone-treated children in the meta-analysis experienced EPS, compared with 30 of 340 (9%) children treated with placebo. A meta-analysis of five RCTs of aripiprazole (3) found that aripiprazole-treated children had a higher OR of EPS compared with the placebo group, with an OR of 3.70 (P<0.0001). One hundred fifty-nine of 629 (25%) aripiprazole-treated children in the meta-analysis experienced EPS, compared with 26 of 323 (8%) placebo-treated children (3). Trials comparing risperidone with olanzapine in the treatment of adolescent psychotic disorders found high rates of anticholinergic treatment for EPS in both groups. Forty per cent of children treated with risperidone and 27% of children treated with olanzapine required anticholinergic therapy in these trials (4,5). Clinicians need to remain aware of the potential for these reactions to occur, and should learn how to recognize and treat them, if necessary.

METHODS

The treatment recommendations are based on the assumption that the treating physician has completed an appropriate diagnostic assessment and that treatment with an SGA is appropriate and necessary. The published literature, key informant interviews and discussions with panel members and stakeholder partners, including community paediatricians, psychiatrists, family physicians and parents, were used to identify key clinical areas of guidance and preferences on format for recommendations of the present guidelines.

The evidence base consisted of systematic reviews of the literature on EPS caused by SGAs in children (3), and the treatment of EPS of antipsychotics. For each clinical question, recommendations were based on evidence and expert opinion, with consideration of values for outcomes and parent preferences. Draft recommendations were presented to a guideline panel consisting of experts in neurology, psychiatry, paediatrics, endocrinology, cardiology, nephrology and family medicine. Members of the guideline panel evaluated the information gathered from the systematic review and used a nominal group process to reach consensus on treatment recommendations. The recommendations were revised to reflect the comments made by the panel. Once complete, the guideline document was externally reviewed by two members of the Movement Disorders Society (neurologists Dr Anthony Lang and Dr Donald Gilbert), and by committee members of the Canadian Paediatric Society.

RESULTS AND RECOMMENDATIONS

Neurological examination techniques and rating scales for extrapyramidal symptoms

A neurological examination is indicated for any patient taking antipsychotic medications as a part of screening for neurological side effects. Examinations should be conducted at baseline and at follow up-visits as outlined in the monitoring guideline (1). Particular attention should be devoted to the following:

1. Mental status: Is the patient alert and oriented? Is there impairment in the level of consciousness? Are attention, memory and executive functions intact?
2. General observation: Does the patient appear to be slow to move or speak (bradykinetic)? Are there abnormal movements noted at rest? Does the patient seem restless with a constant need to move (akathisia)? Does part or all of the patient's body assume an abnormal posture (dystonia)? Is there excessive salivation (sialorrhea)?
3. Cranial nerves: Does the patient exhibit impairment in extra-ocular movements? Does the patient exhibit sustained gaze deviation (oculogyric crisis)? Is there dysarthria or dysphonia? Does the patient exhibit a decrease in facial expression or a 'mask-like' facies? Are there abnormal movements of the face, mouth, lips, jaw or tongue? Clinicians should ensure that the child removes gum or other food from the mouth before the examination.
4. Motor examination: Does the patient have an increased or a rigid tone? Is cog-wheeling present? Are abnormal movements present? Is there a tremor?
5. Coordination and gait: Are movements slowed? Does the patient have trouble with rapid alternating movements? Is the patient slow to stand from a seated position? Does the patient have a shuffling gait? Is there postural instability?

Several standardized rating scales have been developed to assist the practitioner in the examination of patients for drug-induced movement disorders, and to quantify the abnormalities detected. While the use of these instruments is not essential, clinicians may find them useful as a way of deciding which bedside tests should be performed, and as a way of more reliably quantifying abnormalities to facilitate comparisons between visits. The use of videotaped examinations for this purpose can also be extremely helpful. A description of available rating scales is provided in Appendix 1. We recommend the use of the Extrapyramidal Symptom Rating Scale (6) because it assesses for all types of drug-induced movement disorders.

Antipsychotic-induced movement disorders and specific treatment recommendations

The majority of evidence on the treatment of antipsychotic-induced movement disorders comes from adults with schizophrenia. RCTs of treatments for acute and tardive syndromes have been conducted, although the literature pertaining to children is scarce. Existing review articles on the treatment of antipsychotic-induced movement disorders are out of date, and were written before the widespread use of SGAs (7,8). Given the scarcity of

paediatric data, the recommendations below are made with reference to both the adult and paediatric literature. Descriptions of paediatric data are provided in the text for all cases in which this type of data was available. Given limitations in the generalizability of data from adults to children, these recommendations should be considered on the basis of expert opinion, rather than evidence based, even in circumstances in which the level of evidence from adult studies is 'high'. While many of the treatments listed have been used routinely in clinical practice in children for various indications, some medications (eg, mirtazapine and amantadine) have not been used routinely in paediatrics. Practitioners should consult local experts in the field before considering any medication in which dosing parameters in children have not been established or that do not have an established use in paediatric populations.

The *Diagnostic and Statistical Manual* (DSM) criteria for neuroleptic-induced acute dystonia, akathisia, parkinsonism and tardive dyskinesia are listed in Appendixes 2,3,4 and 5, in addition to a description of tardive dystonia and tardive akathisia. Because the DSM uses the term 'neuroleptic' rather than 'antipsychotic' in the definitions of the antipsychotic-induced movement disorders, the nomenclature has been repeated here. Treatment recommendations are provided for each type of movement disorder. The level of evidence (LOE) associated with treatment recommendations are provided. RCTs are considered to be 'high' levels of evidence, observational studies are 'low' and any other evidence (retrospective study, case series or case report) are 'very low'. A summary of medications for the treatment of neurological side effects and recommended dosages in children are provided in Table 1. Recommendations in the present guidelines are numbered; the recommendations listed earlier are those that should normally be considered first. This hierarchy is based on expert opinion rather than on the LOE. Many of the treatments used for the management of antipsychotic-induced movement disorders evolved before modern day clinical trial methodology (eg, anticholinergic agents for acute dystonic reactions), making the LOE for many treatments low despite decades of favourable clinical experience. In general, conservative measures to manage neurological complications of SGAs in children are preferable, ie, discontinuing or lowering the dose of the antipsychotic, rather than the use of cointerventions. Clinicians are encouraged to consult with local experts before starting cointerventions without adequate clinical experience.

Treatment recommendations for neuroleptic malignant syndrome (NMS) are not discussed in the present article. Please refer to a recent systematic review (9) on NMS in children on SGAs, and a treatment algorithm for NMS (10).

Neuroleptic-induced acute dystonia (Appendix 2)

Neuroleptic-induced acute dystonia, or also known as acute dystonic reactions, are seen within days of starting or increasing the dose of an antipsychotic. Dystonic movements are sustained muscle contractions causing twisting, repetitive movements and abnormal postures. In neuroleptic-induced acute dystonia, the cranial, neck and trunk muscles are preferentially affected, although the limbs may also be involved. Typical acute dystonic reactions consist of retrocollis, extension of the trunk, deviation of the eyes, forced jaw opening and tongue protrusion, although symptoms vary among individuals. A meta-analysis of the risk of acute EPS with intramuscular antipsychotics confirmed that SGAs are associated with a significantly lower risk of acute dystonia (RR 0.19 [95% CI 0.10 to 0.39]) and anticholinergic use (RR 0.19 [95% CI 0.09 to 0.43]) compared with haloperidol (11). Given the serious discomfort these reactions cause, and the anxiety they provoke regarding future antipsychotic use, it is important to maintain a high degree of awareness of this potential complication.

Treatment recommendations for neuroleptic-induced acute dystonia:

1. Administer diphenhydramine (LOE high) (12,13) or an anticholinergic (benztropine and biperiden) (LOE very low). The patient and family can be advised that if an acute dystonic reaction occurs, they can self-administer an oral dose of diphenhydramine while seeking medical care. Symptoms will resolve within minutes with parenteral therapy. Repeat doses may be required if no response is seen within 30 min. Intravenous diazepam can be used as an alternative therapy (LOE high) (12). Treatment for two to five days to prevent recurrence may be considered.
2. If ongoing antipsychotic treatment is required, lower the dosage of medication. Co-administration of the antipsychotic with an anticholinergic may be considered (LOE high) (14).

Neuroleptic-induced acute akathisia (Appendix 3)

Akathisia is a term used to describe a state of excessive restlessness with a need to move; symptom relief is achieved with movement. Patients complain of feelings of inner tension or restlessness. Patients will engage in movements such as shaking or rocking of the legs and trunk, pacing, marching in place, rubbing the face or moaning to relieve their discomfort. Young children are not always able to articulate the symptoms of akathisia. Children may describe vague sensations of internal restlessness, discomfort or anxiety, or parents may state that the child appears anxious, or is more irritable or agitated.

Treatment recommendations for neuroleptic-induced acute akathisia are made with the treatment recommendations for neuroleptic-induced parkinsonism, because the initial treatment approach is similar.

Neuroleptic-induced parkinsonism (Appendix 4)

Neuroleptic-induced parkinsonism is a dose-dependent adverse effect of antipsychotic therapy. Manifestations can be indistinguishable from idiopathic Parkinson's disease, with patients displaying features such as classic resting tremor, rigidity, slowness of movement, shuffling gait or unilateral symptoms. A fine, rhythmic perioral tremor may occur (termed 'rabbit syndrome'). It is important to note that neuroleptic-induced parkinsonism can take months to resolve after withdrawal of the offending agent.

Treatment recommendations for neuroleptic-induced acute akathisia or parkinsonism

1. Is the SGA being co-administered with a first-generation antipsychotic? There is a higher risk of EPS in children on first-generation or multiple antipsychotics (15,16) (LOE low). Consider tapering and discontinuing the first-generation antipsychotic.
2. Is the lowest effective dosage of the SGA being used? There is a greater risk of EPS in children on higher doses of risperidone versus lower doses (17) (LOE high). Consider lowering the dosage.
3. Consider switching the current SGA to quetiapine or clozapine – these SGAs have a lower propensity for EPS (18)(LOE high). An open, prospective study in chronic neuroleptic-resistant schizophrenic patients with coexisting parkinsonism and chronic akathisia found a 69% improvement in parkinsonism and a 78% improvement in chronic akathisia after 18 weeks of clozapine therapy (19) (LOE low).

TABLE 1
Medication used to treat neurological complications caused by neuroleptics

Medication (ref)	Paediatric dosage	Indication(s)
Benztropine (68)	0.02 mg/kg/dose to 0.05 mg/kg/dose one to two times/day; usual dose is 0.5 mg to 2 mg two times/day; use in children younger than three years of age should be limited to life-threatening emergencies	Acute dystonic reactions, parkinsonism, akathisia
Diphenhydramine (68)	5 mg/kg/day or 150 mg/m^2/day in divided doses every 6 h to 8 h	Acute dystonic reactions
Biperiden (69)	0.04 mg/kg/dose intramuscular injection (maximum 2 mg) every 30 min to a maximum of four doses in a 24 h period	Acute dystonic reactions
Propranolol (70)	1 mg/kg/day to 2 mg/kg/day divided every 8 h (usual adult dose is 80 mg/day to 320 mg/day)	Akathisia
Clonazepam (68,70)	<30 kg: start at 0.01 mg/kg/day divided two or three times/day; can increase every three to seven days; usual dose is 0.1 mg/kg/day to 0.2 mg/kg/day divided three times/day; not to exceed 0.2 mg/kg/day >30 kg: start at 0.25 mg to 0.5 mg at bedtime and titrated; maintenance dose is 0.05 mg/kg/day to 0.2 mg/kg/day; do not exceed 6 mg/day Clinicians should warn parents of possible paradoxical agitation with the use of benzodiazepines in children (71,72)	Akathisia, tardive dyskinesia
Mirtazapine (68)	Paediatric dose recommendations unavailable (adult dose: 7.5 mg nightly, titrate up to 15 mg/day to 45 mg/day)	Akathisia
Amantidine (70)	Start at 50 mg/day and increase weekly to 50 mg two to three times/day	Parkinsonism
Tetrabenazine (70)	Start 12.5 mg daily; increase by 12.5 mg/day every three to four days; usual dose is 50 mg/day to 150 mg/day; maximum dose is 200 mg/day	Tardive dyskinesia, tardive dystonia, tardive akathisia
Branched chain amino acids (45)	222 mg/kg given three times/day	Tardive dyskinesia
Levetiracetam (68)	Start 10 mg/kg/dose given twice daily; increase every two weeks by 10 mg/kg/dose given two times/day; maximum 60 mg/kg/day	Tardive dyskinesia
Trihexyphenidyl (70)	0.5 mg/day to 1 mg/day and increase by 1 mg every three to five days; usual effective dose is 6 mg/day to 60 mg/day	Tardive dystonia, parkinsonism, acute dystonic reaction
Baclofen (68)	<2 years of age: 10 mg to 20 mg daily divided every 8 h; titrate dose every three days in increments of 5 mg/day to 15 mg/day to a maximum of 40 mg daily Two to seven years of age: 20 mg to 30 mg daily divided every 8 h; titrate dose every three days in increments of 5 mg/day to 15 mg/day to a maximum of 60 mg daily ≥8 years of age : 30 mg to 40 mg daily divided every 8 h; titrate dosage as above to a maximum of 120 mg daily	Tardive dystonia
Lorazepam (69)	0.02 mg/kg oral/intravenous/intramuscular every 4 h to 8 h; not to exceed 2 mg per dose Clinicians should warn parents of possible paradoxical agitation with the use of benzodiazepines in children (71,72)	Tardive akathisia
Reserpine (70)	Start 0.25 mg/day and increase by 0.25 mg/day every few days; usual dose is 1 mg/day to 9 mg/day in divided doses	Tardive akathisia, tardive dyskinesia, tardive dystonia

ref Reference

4. Is the patient taking valproic acid, lithium or a selective serotonin reuptake inhibitor? Both valproic acid (20) and lithium (21) can cause tremor, and valproic acid (20), (22,23) can induce parkinsonism (LOE low). Selective serotonin reuptake inhibitors (24) can induce akathisia (LOE low). Consider tapering these medications to help ameliorate symptoms if antipsychotic medication must be continued.
5. Consultation with a neurologist should be strongly considered.
6. If the above measures are ineffective, and antipsychotic therapy must be continued, consider adding an anticholinergic (25-28) (LOE high), propranolol (28) (LOE high), clonazepam (29) (LOE high) or mirtazapine (30) (LOE high) for akathisia. There is an RCT of clonazepam for the treatment of neuroleptic-induced akathisia in adolescents that demonstrated benefit (31) (LOE high). Anticholinergics or amantadine can be added for the treatment of parkinsonism (25-27) (LOE high).

Neuroleptic-induced tardive dyskinesia (Appendix 5)

The word dyskinesia means 'abnormal movements'. While there are several types of tardive syndromes, tardive dyskinesia is the term traditionally used to describe stereotypic, repetitive, abnormal movements of the mouth, lips and tongue, in a pattern that resembles chewing, sucking or lip pursing. Involvement of the distal limbs can also occur in a repetitive pattern, and has been referred to as 'piano playing fingers and toes'. Patients may also display respiratory dyskinesias, with alternating periods of hyperventilation and hypoventilation. Tardive dyskinesia can be suppressed on request; dyskinesias cease when patients speak or bring food to the mouth. Patients are often unaware of the movements. When patients are requested to keep the tongue at rest in the mouth, the tongue is observed to move side to side, and macroglossia can develop.

The incidence of tardive dyskinesia is lower with SGAs in comparison with first-generation antipsychotics. The risk, however, is not absent, and there is evidence that once tardive dyskinesia develops in SGA-exposed patients, it is persistent for more than two years in 80% of patients (32). Clinicians are urged to remain vigilant for tardive dyskinesia symptoms in children who are prescribed SGAs.

Treatment recommendations for tardive dyskinesia

1. Remission is more likely with prompt discontinuation of antipsychotic therapy. If discontinuation is not possible, consider lowering the antipsychotic dosage. In patients with long-standing tardive dyskinesia, lowering or discontinuing medication may initially exacerbate or unmask tardive dyskinesia symptoms (33). This initial worsening can persist for weeks or months.
2. Discontinue anticholinergic medication if patient is taking concurrently; anticholinergics may exacerbate tardive dyskinesia (34) (LOE high).
3. Consider switching antipsychotic to clozapine, which has been reported in open-label studies to ameliorate tardive dyskinesia (19,35,36) (LOE low). A case report discusses two adolescents with schizophrenia who experienced a beneficial effect with clozapine for tardive dyskinesia (37).
4. Consultation with a neurologist should be considered.
5. Consider treatment of tardive dyskinesia with tetrabenazine (LOE very low) (38,39) or clonazepam (40) (LOE high). Clinical experience with tetrabenazine suggests that it provides the greatest clinical benefit for tardive dyskinesia symptoms, although RCTs are lacking (LOE very low). Vitamin E may prevent deterioration of tardive dyskinesia, but there is no evidence that it improves symptoms (LOE high) (41). More recently, two open-label studies (42,43) and one RCT (44) found levetiracetam to be effective for the treatment of tardive dyskinesia (LOE high). There is a two-week prospective, open-label study of branched chain amino acids for the treatment of tardive dyskinesia in children, which suggests some benefit (45) (LOE low).

Withdrawal dyskinesias

Withdrawal dyskinesias (also known as the withdrawal emergent syndrome) are choreiform movements that have been reported in children, and can be seen when antipsychotics are discontinued abruptly (46,47). The movements resemble Sydenham's chorea, with brief abnormal movements that flow from one muscle group to another in a random pattern. Withdrawal dyskinesias most commonly affect the limbs, trunk and neck, and will disappear spontaneously within several weeks. If withdrawal dyskinesias occur, the withdrawn antipsychotic medication can be restarted to suppress the movements, and can be tapered over a longer time period. In contrast to tardive dyskinesia, withdrawal dyskinesias are self-limited and tend to resolve over weeks.

Neuroleptic-induced tardive dystonia

Tardive dystonia is considered to be a distinct subtype of tardive dyskinesia, and is discussed separately because the clinical manifestations are unique, as is the recommended therapy. The term tardive dystonia is used to describe sustained, slow, involuntary twisting movements affecting the limbs, trunk, neck or face, associated with neuroleptic therapy. This is distinct from classic tardive dyskinesia – a term usually used to describe oral choreiform/stereotypic movements. Tardive dystonia can be generalized, segmental or focal. Common manifestations include retrocollis, facial grimacing affecting the lower face, opisthotonic trunk extension and hyperpronation of the arms. In the largest described case series (48), the average duration of exposure to antipsychotics before the onset of tardive dystonia was 3.7 years (range three days to 20 years). Of the 42 cases described, eight were 18 years of age or younger at the time of onset of tardive dystonia symptoms. Younger individuals were more likely to have generalized dystonia. Tardive dystonia has been reported as a consequence of SGA treatment using olanzapine (49,50), risperidone (51,52), aripiprazole (53) and ziprasidone (54,55), and typically affects younger patients.

Treatment recommendations for tardive dystonia

1. Remission is more likely with prompt discontinuation of antipsychotic therapy. Given the much greater disability associated with tardive dystonia in comparison with classic orolingual tardive dyskinesia, strong consideration should be given to discontinuation of the medication.
2. If continued antipsychotic therapy is necessary, consider switching to clozapine. Open-label studies and case reports have shown that this may ameliorate the dystonia (36,56,57) (LOE low). A case of tardive dystonia was reported involving an adolescent who was initially treated with thioridazine, and whose symptoms were successfully relieved with clozapine (58).
3. If the antipsychotic medication can be discontinued, taper off the medication and treat the dystonia with an anticholinergic such as trihexyphenidyl. There are case reports of adolescents with tardive dystonia who were successfully treated with anticholinergic therapy (52,59) (LOE very low).
4. If there is an inadequate response to anticholinergic medication, consultation with a neurologist is recommended. Treatments that may be considered include botulinum toxin injections for focal dystonia (eg, cervical dystonia, lingual dystonia) (60) (LOE very low), tetrabenazine (39) (LOE very low) or baclofen (61) (LOE very low). Intrathecal baclofen (62) can be used for refractory tardive axial dystonia (LOE very low). Several case reports suggest that bilateral pallidal deep brain stimulation is effective for severe treatment refractory tardive dystonia (63) (LOE very low).

Neuroleptic-induced tardive akathisia

Persistent akathisia may occur as a subtype of tardive dyskinesia. Persistent akathisia is defined as being present for at least one month when the patient is on a constant dose of a neuroleptic. Tardive akathisia may occur in association with typical orolingual tardive dyskinesia or tardive dystonia. Movements affecting the legs are most common, such as marching in place while standing, and while sitting crossing/uncrossing the legs, rapidly abducting and adducting the legs, or pumping the legs up and down. Trunk movements include repetitive anterior to posterior rocking while sitting. Arm movements include smoothing the hair with the palm of the hand, rubbing the face with the palm or back of the hand, folding and unfolding the arms, and repetitively rubbing the anterior surface of the thighs. Simple vocalizations, such as grunting or moaning, have been described.

Treatment recommendations for tardive akathisia

1. If possible, withdrawal of the antipsychotic should be attempted to observe whether symptoms resolve.
2. Tardive akathisia does not consistently respond to medication. One case series of 30 treated patients suggest that the best results were obtained with tetrabenazine, reserpine and lorazepam (64) (LOE very low). Some case reports have shown improvement with propranolol (65) (LOE very low), a combination of lorazepam and the anticholinergic medication procyclidine (66) (LOE very low), and with switching antipsychotic therapy to clozapine (67) (LOE very low).

CONCLUSION

These treatment recommendations have been created to assist practitioners prescribing antipsychotics to children. It is our hope that it will facilitate recognition of neurological complications if they occur, and provide some guidance on the approach to treatment. Where feasible, consolidation of the monitoring and intervention tasks into protocols or policies in a multidisciplinary environment may have some advantages. The specialized monitoring procedures discussed in the CAMESA monitoring guideline and described further in the present manuscript may benefit from standardization – specialized health records could be developed, and access to consultation ensured. Clinicians with limited experience in monitoring patients on antipsychotics may find consultation with a neurologist, movement disorder specialist or psychiatrist very helpful if abnormal movements develop in this setting. There is a need for empirical data and further research on the management of neurological complications of antipsychotic use in children.

While rates of EPS caused by SGAs are lower than first-generation high-potency agents, these side effects are not absent, and can be seen in children. It is important that clinicians be aware of the potential of these medications to induce neurological side effects, and exercise a high degree of vigilance when they are prescribed.

APPENDIX 1

None of the rating scales described below have been validated or developed specifically for paediatric use. Our consensus group did not believe that this precluded the usefulness of these instruments in children. All four instruments are routinely used in paediatrics in clinical trials and in clinical care. Administration times vary between instruments. The Extrapyramidal Symptom Rating Scale, the longest and most comprehensive of the four rating scales, takes approximately 10 min to administer in a cooperative child.

The Abnormal Involuntary Movement Scale (AIMS) is a clinical rating instrument for the assessment of tardive dyskinesia (1). The original version includes 10 items scored on a 5-point scale (possible scores 0 to 4, with 0 representing 'none' and 4 representing 'severe'). Four items pertain to facial and oral movements, two items pertain to extremity movements, one item pertains to trunk movements and three items are global judgements.

The Simpson Angus Scale (SAS) is a 10-item rating scale for the assessment of neuroleptic-induced parkinsonism. Each item is rated on a 5-point scale (possible scores 0 to 4), with definitions for each rating scale score provided. The domains assessed include gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabellar tap, tremor and salivation. Good internal consistency and inter-rater reliability has been demonstrated for this instrument in patients with schizophrenia (2). The instrument can discriminate between patients with and without drug-induced parkinsonism (3).

The Barnes Akathisia Scale (BAS) is a four-item rating scale to assess akathisia (4). Each item is rated on a 4-point scale (0 to 3). There is one item assessing objective signs, two subjective items assessing awareness and distress related to restlessness, and a global clinical assessment. Definitions of each severity rating are provided.

The Extrapyramidal Symptom Rating Scale (ESRS) (5) was developed to assess four types of drug-induced movement disorders: parkinsonism, akathisia, dystonia and tardive dyskinesia. It consists of four subscales and four clinical global impression severity scales for each type of movement disorder. The four subscales include the following:

I. A questionnaire of extrapyramidal symptoms or drug-induced movement disorders
II. An examination of parkinsonism and akathisia
III. An examination of dystonia
IV. An examination of dyskinesia

An explicit scoring system for ratings on each scale is provided. Inter-rater reliability is high, with mean item correlation coefficients of 0.80 to 0.97; strong concordance between the AIMS and ESRS dyskinesia scale ratings has been demonstrated (6). The major advantage of the ESRS over the other rating scales is that it assesses all types of extrapyramidal symptoms. It is the only scale that assesses for the presence of dystonia. While choosing between scales should be based on physician preference, we recommend the use of the ESRS because it assesses for all types of drug-induced movement disorders (see reference 5 for ESRS instrument for clinical use).

APPENDIX 2

The DSM-IV criteria (7) for neuroleptic-induced acute dystonia are as follows:

A. One (or more) of the following signs or symptoms has developed in association with the use of neuroleptic medication:
   1. Abnormal positioning of the head and neck in relation to the body (eg, retrocollis or torticollis).
   2. Spasms of the jaw muscles (trismus, gaping or grimacing).
   3. Impaired swallowing (dysphagia), speaking or breathing (laryngeal-pharyngeal spasm, dysphonia).
   4. Thickened or slurred speech due to hypertonic or enlarged tongue (dysarthria or macroglossia).
   5. Tongue protrusion or tongue dysfunction.
   6. Eyes deviated up, down or sideward (oculogyric crisis).
   7. Abnormal positioning of the distal limbs or trunk.
B. The signs or symptoms in criterion A developed within seven days of starting or rapidly raising the dose of a neuroleptic medication, or of reducing a medication used to treat (or prevent) acute extrapyramidal symptoms (eg, anticholinergic agents).
C. The signs or symptoms in criterion A are not better accounted for by a mental disorder (eg, catatonic symptoms in schizophrenia). Evidence that the symptoms are better accounted for by a mental disorder might include the following: the symptoms precede the exposure to neuroleptic medication or are not compatible with the pattern of pharmacological intervention (eg, no improvement after neuroleptic lowering or anticholinergic administration).
D. The symptoms in criterion A are not due to a non-neuroleptic substance or a neurological or other general medical condition. Evidence that the symptoms are due to a general medical condition might include the following: the symptoms precede exposure to the neuroleptic medication, unexplained focal neurological signs are present, or the symptoms progress in the absence of change in medication.

APPENDIX 3

The DSM-IV criteria (7) for the diagnosis of neuroleptic-induced acute akathisia are as follows:

A. The development of subjective complaints of restlessness after exposure to a neuroleptic medication.
B. At least one of the following is observed:
   1. Fidgety movements or swinging of the legs.
   2. Rocking from foot to foot while standing.
   3. Pacing to relieve restlessness.
   4. Inability to sit or stand still for at least several minutes.

C. The onset of the symptoms in criteria A and B occurs within four weeks of initiating or increasing the dose of the neuroleptic, or of reducing medication used to treat (or prevent) acute extrapyramidal symptoms (eg, anticholinergic agents).
D. The symptoms in criterion A are not better accounted for by a mental disorder (eg, schizophrenia, substance withdrawal, agitation from a major depressive or manic episode or hyperactivity in attention-deficit/hyperactivity disorder). Evidence that symptoms may be better accounted for by a mental disorder might include the following: the onset of symptoms preceding the exposure to the neuroleptics, the absence of increasing restlessness with increasing neuroleptic doses, and the absence of relief with pharmacological interventions (eg, no improvement after decreasing the neuroleptic dose or treatment with medication intended to treat the akathisia).
E. The symptoms in criterion A are not due to a non-neuroleptic substance or a neurological, or other general medical condition. Evidence that symptoms are due to a general medical condition might include the onset of the symptoms preceding the exposure to neuroleptics or the progression of symptoms in the absence of a change in medication.

APPENDIX 4

The DSM-IV diagnostic criteria (7) for neuroleptic-induced parkinsonism are as follows:

A. One (or more of the following signs or symptoms has developed in association with the use of neuroleptic medication:
   1. Parkinsonian tremor (ie, a coarse, rhythmic, resting tremor with a frequency between three and six cycles per second, affecting the limbs, head, mouth or tongue)
   2. Parkinsonian muscular rigidity (ie, cogwheel rigidity or continuous 'lead pipe' rigidity)
   3. Akinesia (ie, a decrease in spontaneous facial expressions, gestures, speech or body movements)
B. The symptoms in criterion A developed within a few weeks of starting or raising the dose of a neuroleptic medication, or reducing a medication used to treat (or prevent) acute extrapyramidal symptoms (eg, anticholinergic agents).
C. The symptoms in criterion A are not better accounted for by a mental disorder (eg, catatonic or negative symptoms in schizophrenia, psychomotor retardation in a major depressive episode). Evidence that the symptoms are better accounted for by a mental disorder might include the following: the symptoms precede the exposure to neuroleptic medication or are not compatible with the pattern of pharmacological intervention (eg, no improvement after lowering the neuroleptic dose or administering anticholinergic medication).
D. The symptoms in criterion A are not due to a non-neuroleptic substance or a neurological or other general medical condition (eg, Parkinson's disease or Wilson's disease). Evidence that the symptoms are due to a general medical condition might include the following: the symptoms precede exposure to neuroleptic medication, unexplained focal neurological signs are present, or the symptoms progress despite a stable medication regimen.

APPENDIX 5

The DSM-IV criteria (7) for neuroleptic-induced tardive dyskinesia are as follows:

A. Involuntary movements of the tongue, jaw, trunk or extremities have developed in association with the use of the neuroleptic medication.
B. The involuntary movements are present over a period of at least four weeks and occur in any of the following patterns:
   1. Choreiform movements (ie, rapid, jerky, nonrepetitive).
   2. Athetoid movements (ie, slow, sinuous, continual).
   3. Rhythmic movements (ie, stereotypies).
C. The signs of symptoms in criteria A and B develop during exposure to a neuroleptic medication or within four weeks of withdrawal from an oral (or within eight weeks of withdrawal from a depot) neuroleptic medication.
D. There has been exposure to neuroleptic medication for at least three months (one month if 60 years of age or older).
E. The symptoms are not due to a neurological or general medical condition (eg, Huntington's disease, Sydenham's chorea, spontaneous dyskinesia, hyperthyroidism or Wilson's disease), ill-fitting dentures or exposure to other medications that cause acute reversible dyskinesia (eg, L-dopa, bromocriptine). Evidence that the symptoms are due to one of these etiologies might include the following: the symptoms precede the exposure to the neuroleptic medication or unexplained focal neurological signs are present.
F. The symptoms are not better accounted for by a neuroleptic-induced acute movement disorder (eg, neuroleptic-induced acute dystonia or neuroleptic-induced acute akathisia).

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